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09/445,201	04/12/00	BREIER G	VOSS1110

EXAMINER	
DRABIK,C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/445,201	Applicant(s) BREIER ET AL.	
	Examiner Christopher Drabik	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *12,15,16,25-33 and 36-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,14,17-24,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants response to the Restriction Requirement has been received and entered as paper NO. 13. Applicants have elected Group I and request the rejoinder of Group III stating that Group I and III are linked by the same inventive construct. The examiner respectfully disagrees with the applicants request for rejoinder for the following reasons. The practice of restriction regarding 371 applications allows applicants the claimed product and first method of use and method of making (See 37 CFR 1.47 9b) and (d)). The examiners restriction of the claims clearly follows this practice. The restricted invention of Group I consists of claims to a modified vector and it's use as a pharmaceutical composition (Claim 24.) Claims for the use of a pharmaceutical composition encompass claims 34 and 35. The use of the vector for *preparation* of a pharmaceutical composition are distinct from the use of the composition as a treatment and include making other substances to serve as the pharmaceutical composition because the claims are incomplete. Hence claims 36-39 are appropriately considered a separate invention. For the foregoing reasons the Restriction Requirement is deemed proper and is made **FINAL**.

Claims 1- 41 are pending in the instant application. The claims of elected Group I, claims 1-11, 13, 14 , 17-24, 34 and 35 are examined herein. Claims 12, 15, 16, 25-33 and 36-40 are withdrawn.

In the Specification

Figure 1 is objected to because the figure is unclear in delineating the location of the enhancer within the first intron

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13,14, 17-24, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "...an intron of a gene homologous to..." It is unclear what applicants consider as the degree of homology which could be used to ascertain the metes and bounds of the claim. While the specification discusses homology (see page 7, lines 6 – 17) it remains unclear as to what applicants mean by, for example, conferring "substantially the same expression pattern." No guidance is provided with regard to what applicants consider "substantially the same" such that the limitations of homology can be evaluated. Claims 2-11, 13,14, 17-24, 34 and 35 depend from claim 1 and are bound to the limitations of claim 1.

Claims 1-11, 13,14, 17-24, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the term "capable." Use of this term is unclear because it merely suggests the possibility of an

event occurring, but does not afford any certitude of that event . Claims 2-11, 13,14, 17-24, 34 and 35 depend from claim 1 and are bound to the limitations of claim 1.

Claims 3 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 3 and 9 recite "...sequence which is conserved in..." referring to sequence similarities. It is unclear what degree of conservation between sequences is sufficient to meet the limitation of the claim.

Claims 3 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 and 9 recite a DNA sequence comprising an "anologue or derivative of a nucleotide sequence." It is unclear what applicants mean by analogue. For example it is unclear what degree of similarity between two sequences is sufficient to deem them analogs. The term derivative is unclear because it merely states a starting material, but does not define in sufficient detail what the end product.

Claim 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13 and 14 depend from non-elected claim 12. For examination purposes, Claims 13 and 14 will be assumed to depend from claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13,14, 17-24, 34 and 35 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

While the specification provides adequate written description for the claimed invention (methods and products) only with regard to the regulatory region within the first intron of the murine VEGF flk-1 receptor, the specification fails to describe the other species within the genus of regulatory sequences, encompassed in the claims with particularity to indicate that applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art **as of Applicants effective filing date**. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed

drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiments of any and all regulatory sequences other than those specifically described within the first intron of the murine VEGF flk-1 receptor , lack a written description. The specification fails to describe what elements other than those isolated from mouse, fall into this genus when and constructed and used as claimed, and it was unknown as of Applicants' effective filing date that any of these regulatory sequences would have the properties of murine VEGF flk-1 receptor. The skilled artisan cannot envision the detailed chemical structure of all of the encompassed transcriptional regulatory elements isolated from any and all species, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Claims 20- 23, 24, 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Claims 20-23 24, 34 and 35 encompass or are completely drawn to therapeutic gene transfer. The nature of the proposed therapy is through the use of vectors apparently targeted for expression in endothelial cells by virtue of VEGF receptor regulatory sequences. Applicants broadly claim vascular disease as the object of their therapeutic intervention. In addition they claim therapies which reduce the proliferation of smooth muscle cells. The route of administration claimed is "contacting an artery". The breadth of the claims encompass any vector, any vascular disease, any method of administration and the transfer of any gene. Claims 20-23 are directed to cells and encompass and encompass cell in vivo as well as in vitro when read in light of the specification. Insertion of "isolated" or "cultures" into the claim would obviate rejections over these claims.

Although the field is rapidly developing, the practice of gene therapy remains unproven. At the time of filing, gene therapy could not be practiced even by those of considerable skill in the art. Verma et al in reviewing the state of gene therapy sum the progress by stating: "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (Nature (1997) vol. 389, p. 239, col. 1, 2nd paragraph). W. French Anderson concluded: "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human diseases [Nature, vol. 392:(Supp.), 1998, p. 25, first paragraph]...[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. More recently, Patterson, directing remarks to the Senate subcommittee on Public Health stated :"To date more than 4000 patients have participated in gene therapy studies (in 372 NIH registered trials)... Only one percent of the trials (3 protocols) have progressed to phase III efficacy studies. Thus, most human gene therapy clinical trials have been focused on safety rather than efficacy. For this reason, it is perhaps more appropriate to refer to this technology as gene "transfer" rather than 'gene therapy', until there is more evidence for the therapeutic benefit of this technology." (Patterson A (2000) http://www4.od.nih.gov/oba/patterson2-00.pdf see page 2, 2nd full paragraph).

Verma further states that "[t]he Achilles heel of gene therapy is gene delivery...and [t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression... [a]lthough there are reagents that increase the

efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addressed" (Nature, vol. 389, 1997, p. 239, col. 3, 2nd). Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. explains, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. [See Eck et al Gene-Based Therapy in *The Pharmaceutical Basis of Therapeutics*, 9^{th} *ed* (1996) McGraw Hill ¶ bridging pages 81- 82.]

While the claimed invention is broadly drawn to pharmaceutical compositions and methods of treating vascular diseases by gene transfer methodologies employing regulatory sequences, applicants have only demonstrated that reporter gene constructs can be expressed using the regulatory sequences of the intron of flk-1 gene and only when the gene is transferred to embryos. No demonstration of any construct capable of transferring a gene to an animal is demonstrated. Hence, the disclosure provides no basis for claiming gene transfer other than in the context of generating a transgenic animal. The demonstration of reporter gene expression does no sufficiently address the problems of transient expression or demonstrate that a therapeutic gene can be

expressed at a high enough level sufficient to effect any disease state. Furthermore, the scope of the claims encompasses any form of administration. While, applicants have demonstrated that the intron apparently is specific for the modulation of genes in endothelial cells, applicants have not shown that a vector comprising the intron can specifically target endothelial cells, hence, it is unclear as to whether the claimed invention would be able to deliver a specific gene in sufficient enough quantities to insure levels transgene expression that would effect a disease state.

The degree of experimentation required to enable an invention is considered to be inversely proportional to the unpredictability in the art. Although there is an extremely high level of unpredictability in the field and considerable technical difficulties to surmount, applicants have not demonstrated the in vitro transfer of a "therapeutic" gene let alone demonstrated the in vivo benefit of such a transfer. Given the nature of the claimed subject matter, the lack of adequate guidance and the lack of working examples demonstrating gene therapy, it is not possible for one of skill in the art to use the invention commensurate with the scope of the claims.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1- 7, 9, 10, 13,14, 17, 18, 20, 21, 22 and 24 rejected under 35 U.S.C. 102(b) as being clearly anticipated by Patterson et al. (WO97/00957)

Claim 1- 7, 9, 10, 13, 14, 17, 18, 20, 21, 22 and 24 of the instant application are drawn to a regulatory sequence of an intron of the vascular endothelial growth factor receptor –2 gene (flk-1) or of an intron of a gene "homologous" to (flk-1) wherein said regulatory sequence is linked operatively to a heterologous DNA sequence. The breadth of the claim includes any regulatory sequences which are capable of regulating expression of flk-1 or genes homologous to flk-1. This includes tyrosine kinase type receptors which bind vascular endothelial growth factor (VEGF) such as flt-1. It is important to note that both receptors are predominantly expressed in endothelial cells, hence both flt-1 and flk-1 promoters and regulatory sequences are apparently specific for endothelial cells. The art cited herein is drawn to flk-1, however, given the extreme breadth of the claims, references citing vectors comprising flt-1 regulatory sequences, for example the X reference (Williams et al WO9/17359) cited in the International Search Report of the corresponding PCT, also clearly reads on the claims. It is further important to note that the claims are drafted such that the regulatory sequences can be derived from any sequence which regulates expression of a VEGF receptor.

Patterson et al disclose regulatory sequences of human flk-1 which confer endothelial specific expression and are linked to a heterologous nucleic acid (see e.g. face of patent and Claims 1 and 6.) The disclosure of Patterson indicates that the regulatory sequences comprise at least GATA binding and SP-1 binding sites. Other

non-disclosed binding sites may also inherently be present in the sequence disclosed by Patterson et al. The constructs disclosed encode a portion of the first intron, the regulatory sequences include a promoter and heterologous nucleic acid in the form of the luciferase gene (see page 14.) The promoter is both hypoxia inducible and of a growth factor receptor. The constructs were based on commercially available vectors (Promega) encoding luciferase with a 3' untranslated region standard for efficient transcript expression in reporter gene constructs. Hence, claims 1-7, 9, 10 and 14 are clearly anticipated by the disclosure of Patterson et al.

The sequences disclosed by Patterson et al are for use in a vector which confers endothelial specific expression of a polypeptide. Said polypeptide can be P21 cell cycle inhibitor, nitric oxide synthase, interferon-γ, plasminogen activator or atrial natiuretic polypeptide (see claims 7-11.) Claim 12 of WO97/00957 recites an endothelial cell which comprises the vector. Standard isolation and manipulation procedures in molecular biology include the re-suspension of nucleic acids in water or physiologic buffers. Nucleic acids re-suspended as described can be considered pharmaceutical composition since they may be administered to subjects. Hence claims 13, 17, 18, 20, 21, 22 and 24 are clearly anticipated by Patterson et al.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over (WO97/00957), and Ema et al

Patterson et al teach the use of vascular endothelial growth factor receptor regulatory sequences for endothelial specific expression of polypeptides. In there disclosure they claim a number of specific protein which could be regulated by the flk-1 sequences. Patterson et al does not explicitly teach the

Ema et al disclose the bHLH-PAS factor. The authors disclose that this factor is similar in sequence to hypoxia inducible factor 1-α (HIF-1α). In subsequent literature bHLH-PAS is also referred to as HIF-2α. Explicit in the disclosure of Ema et al is that the expression of the hypoxia inducible factors 1 and 2 have been of general interest in the field. (See introduction.) And further that HIF-1α and 2α are hypoxic-responsive mediator of the expression of a number of different proteins. Therefore an art accepted goal has been to achieve a better understanding of the effects of HIF-2α.

It is well known in the art that endothelial cells react to hypoxia. Given that a desired goal of the art is to gain a better understanding of the effect of hypoxia on endothelial cells the use of an endothelial specific promoter construct containing a modulator of hypoxia related genes would be of obvious utility of one of skill in the art.

Conclusion

Claim 8 is deemed free of the prior art, given the unpredictability inherent in the process as discussed above, and the failure of the prior art to teach or reasonably

suggest the use of the VEGF or PDGF promoter in conjunction with flk-1 regulatory regions.

Claim 11 is deemed free of the prior art in as far as the prior art has not taught the use of flk-1 regulatory regions placed upstream of a heterologous nucleic acid.

Claims 1-7, 9,10, 13, 14 , 17-24, 34 and 35 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on 703- 305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Inquiries of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-305-3015.

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